Slides Prepared by the NephMadness Executive Committee

- Anna Burgner
- Elena Cervantes
- Matthew Sparks
- Samira Farouk
- Anna Vinnikova
- Jeffrey Kott
- Michelle Lim
- Timothy Yau
What To Do

• Review the Regions & Teams on AJKDBlog
• Submit your picks by March 31, 2024, on Tourneytopia
• Discuss on social media using #NephMadness
• Claim CME/MOC credit through NKF PERC by May 31, 2024
The BRP Has Already Chosen the Winning Bracket

To win, predict what the BRP picked & thinks will bring the most practice change to nephrology!

- Tom Oates
- Sylvia E. Rosas
- Bjørn Helge Haug
- Jodi Smith
- Richard Knight
- Matt James
- Michelle A. Josephson
- Kirk Campbell
- Andrea Sofía Alvarez Muñoz
The next 2 slides will help you use Zoom to fill out your group bracket

Pro Tips:
• Submit all brackets at nephmadness.com
• Submit individual & group brackets
• Submit a back-up bracket (2 brackets per person)
• Use “Quick Picks” if you can’t decide!
How to Fill Out Your NephMadness Bracket with Zoom Polls

**Step 1.** Start a new Zoom meeting (as Host)
Click “Polling” then “Add a Question”

**Step 2.** Create 1 question with options A & B.
Click “Save” and check “anonymous”

**Step 3.** Click “Polling” again in your meeting → “Launch Poll”. After all have voted, click “End Poll”

**Step 4.** Fill in the matchup winner based on the results. Click “Re-Launch”

**Step 5.** Click “Continue”

**Step 6.** Repeat steps 4-5 until all 31 matchups are completed. Crown your NephMadness Champion!
The A-B choices would look like this in the bracket:

- Bracket submission March 1 - March 31
- Earn MOC and CME credits
- Open to individuals and/or groups
- Details available at AKDblog.org
- Free to enter
Preeclampsia

Writers:
Gilda Portalatin
Connor Grantham

Experts:
Michelle Hladunewich
Jessica Tangren

Region Execs:
Anna Burgner
Samira Farouk
Preeclampsia: A Pregnancy Specific Hypertensive Disease w/ Multisystem Involvement

- Diagnosis based upon clinical criteria:
  - >20 weeks’ gestation
  - New onset hypertension (SBP >140 OR DBP >90)
    AND
  - New onset proteinuria (>300 mg/24 hours of a spot urine protein: creatinine ratio >0.3 g/g)
    OR
  - End organ dysfunction (thrombocytopenia, liver dysfunction, new renal insufficiency, pulmonary edema, new onset cerebral or visual disturbances)

- Diagnosis is difficult in women with preexisting kidney disease, hypertension, and/or proteinuria

- Understanding the pathophysiology has led to biomarkers to help the diagnosis of and may lead to treatment of preeclampsia, namely the sFLT-1/PIGF ratio
Preeclampsia Pathophysiology

• **Normal development of placenta requires extensive angiogenesis**
  - Normal placenta produces a balance of proangiogenic (VEGF, PlGF) and antiangiogenic factors (sFlt-1)
  - sFLT-1 helps to maintain the appropriate depth of the placenta in the uterine wall
  - PlGF is important for spiral artery remodeling and developing the placental capillary network

• **In preeclampsia a trigger leads to an imbalance with an excess of antiangiogenic factors present**
  - Trigger likely related to placental hypoperfusion/hypoxia/ischemia
  - sFLT-1 levels are increased in women with preeclampsia or those who are soon to develop preeclampsia
  - PlGF levels are decreased in women with preeclampsia or those who are soon to develop preeclampsia

• **Trials ongoing with novel therapeutic strategies based upon this pathophysiology**
  - sFLT-1 ligands, small interfering RNA based therapies to reduce sFLT-1 production, and apheresis paired with columns utilizing monoclonal antibodies to selectively deplete sFLT-1
What is the predictive value of sFlt-1:PIGF Ratio in women with suspected preeclampsia?

Prospective, Multicentre, Observational

sFlt-1:PIGF cut off for prediction of preeclampsia in suspected women (24+0 to 36+6 weeks)

Development cohort (N = 500)  Validation cohort (N = 550)

sFlt-1:PIGF ≤ 38

Negative predictive value (No PE within 1 wk) 99.3% 95% CI 97.9, 99.9

80.0% 95% CI, 51.9, 95.7

78.3% 95% CI, 74.6, 81.7

Sensitivity

Specificity 83.1% 95% CI, 79.4, 86.3

sFlt-1:PIGF > 38

Positive predictive value (PE within 4 wks) 36.7% 95% CI 28.4, 45.7


Conclusion: An sFlt-1:PIGF ratio of 38 or lower can be used to predict the short-term absence of preeclampsia in women in whom the syndrome is suspected clinically.
Preeclampsia Risk Factors, Prevention & Long-Term Sequelae
Preeclampsia Risk Factors

- Preeclampsia affects up to 5% of all pregnancies
- Contributes to 70,000 maternal and 500,000 fetal deaths annually world-wide
- Incidence in preeclampsia increasing, as risk factors increase
- Every woman with CKD is at risk for preeclampsia
- Long term complications include:
  - Increased risk of cardiovascular disease, heart failure, stroke, diabetes, kidney disease, mental health disorders, and vascular dementia

**High Risk**
- Prior history of preeclampsia
- Preexisting chronic hypertension
- Type 1 and Type 2 diabetes mellitus
- Multifetal gestation
- Chronic kidney disease
- Systemic lupus erythematosus
- Antiphospholipid antibody syndrome

**Moderate Risk**
- Nulliparity
- Family history of preeclampsia
- Maternal age of 35 years or older
- Obesity
- Socio-demographic characteristics
- Personal history of being born low birth weight, being small for gestational age, and past pregnancy complications
- In vitro conception
Preeclampsia Prevention

• Two main ways to decrease the risk of preeclampsia:

  1) Low dose Daily Aspirin
     - Recommended for patients with 1 high risk or 2 moderate risk factors
     - Start between 11-13 weeks’ gestation

  2) Treat chronic hypertension in pregnancy to a goal <140/90 mmHg

• In addition, in patients with CKD to decrease risk of preeclampsia:
  – Seen prior to pregnancy and have kidney disease treated and proteinuria suppressed
  – Those with lupus nephritis should be counseled to wait till their nephritis has been quiescent for at least 6 months and be maintained on hydroxychloroquine throughout pregnancy
  – Those with other GN’s should also have been treated and be in remission prior to pregnancy.
CHAP trial: Are there any benefits to treating mild chronic hypertension during pregnancy?

**METHODS**
- Open label, multicenter, randomized trial
- 2408 pregnant women
- Singleton fetus
- Gestational age <23 weeks
- Mild chronic hypertension

**COMPOSITE PRIMARY OUTCOME**
- Preeclampsia with severe features
- Placental abruption
- Fetal/neonatal death
- Preterm birth <35 weeks

**SAFETY OUTCOME**
- Birth weight < 10th percentile for gestational age

<table>
<thead>
<tr>
<th>Control group</th>
<th>Active group</th>
</tr>
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<tbody>
<tr>
<td>No treatment unless SBP ≥ 160 or DBP ≥ 105 mmHg</td>
<td>Labetalol or extended release nifedipine</td>
</tr>
<tr>
<td>Goal: &lt;140/90 mmHg</td>
<td>Goal: &lt;140/90 mmHg</td>
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</tbody>
</table>

- **37%** (aRR: 0.82, 95% CI, 0.74-0.92)
- **10.4%** (aRR: 1.04, 95% CI, 0.82-1.31)
- **30.2%** (11.2%)

**Conclusion:** In pregnant women with mild chronic hypertension targeting a blood pressure <140/90 mmHg was associated with better pregnancy outcomes and no increase in the risk of small for gestational age birth weight.


**VA by Cristina Popa @NephroSeeker**
EFFLUENT EIGHT ROUND

Pick Your Champion for the Preeclampsia Region

Diagnosis and Treatment of Preeclampsia

vs

Preeclampsia Risk Factors, Prevention and Long-Term Sequelae
Animal House 4

Writer:
Tiffany Truong

Expert:
Kelly Hyndman

Region Execs:
Anna Vinnikova
Matt Sparks
Gila Monster
Gila Monster
*Heloderma suspectum*

- **Gila monster** produces venom in modified salivary glands
- **Exendin-4**
  - Similar function and structure with human GLP-1
  - Not cleaved by DPP-4
  - Longer action than GLP-1
  - T1/2 = 1-4 hours
- **Gila monster** = binge-eater, as little as 3-4 times/year
- Stimulates insulin production in the pancreas, only when glucose levels are high (e.g. after meals)

**References:**
- Drucker DJ, The GLP-1 journey, from discovery science to therapeutic impact, J Clin Invest, 2024
- Beck J, Biology of Gila Monsters and Beaded Lizards, 2005
- Yap and Misuan, Exendin 4 from Heloderma Suspectum venom: From discovery to its latest application as type II diabetes combatant, Basic Clin Pharmacol, Toxicol, 2018

VA by Cristina Popa @NephroSeeker
Incretin-based therapies

- **GLP1- R agonists**: Improve BG, BP, proteinuria, weight, inflammation, fibrosis, CV outcomes
- **DPP-4 inhibitors**: Improve BG only
The Gila Monster’s Canteen: The Role of the Urinary Bladder in Water Economy

Gila monster needs adapting to seasonal drought and high temperatures, in the Sonoran desert.

Urinary bladder walls are water permeable.

Absorption of dilute urine from the urinary bladder provides osmoregulatory benefits over 24-48h equaling those associated with drinking.

Gila monster with full urinary bladders dehydrate slower than those with empty bladder.

Conclusion: Dilute urine stored in the urinary bladder of the Gila monster serves as a physiological reservoir, which allows Gila monsters to manage water budgets on a long-term (months) rather than short-term (daily) basis.

Plasma osmolality of Gila monsters that will remain relatively stable March-April, peak just prior to the start of summer monsoon rains in July, and return to March-April levels in August-September during the rainy season.


VA by Cristina Popa @NephroSeeker
Mourning Dove
Why don’t birds get diabetic end-organ damage and shortened lifespans despite persistently elevated serum glucose levels?

Benign hyperglycemia is a shared trait of birds
Glucose levels are 2x similar sized mammals
Glucose levels in birds are generally resistant to diet, hormones and pharmaceuticals

The evolution of benign hyperglycemia in birds coincided with a genomic upheaval

Glucose is taken up by tissues with the help of a family of glucose transport proteins (GLUTs)

Loss of the GLUT4 genes resulted in the remodeling of the insulin-signaling pathway in birds’ tissues

Birds might have also evolved glycation-resistant proteins, including albumin

Resistance to oxidative stress is attributed to higher antioxidants and less free radical production

Conclusion: Birds naturally have blood glucose concentrations that are nearly double levels measured for mammals of similar size. However, overt diabetes in birds is quite rare. Theories attempting to explain high glucose levels in birds include low insulin secretion, reliance on fats and amino acids for energy, and lack of a functional insulin-responsive GLUT4 transport protein. Glycation-resistant proteins prevent tissue damage from the persistent hyperglycemic milieu.


VA by @brian_rifkin
What are the unique features of avian urinary system?

Mammalian nephron:
- Nephrons have loops of Henle that concentrate urine
- Concentration less effective than reptiles
- Up to 30% of nephrons in avian kidneys

Reptilian nephron:
- Nephrons are devoid of loops of Henle, unable to concentrate urine
- Reduced activity when challenged with salt load or water deprivation

Birds have reptilian & mammalian type nephrons

Birds excrete nitrogenous waste as uric acid

Uric acid

Renal portal system:
- Low pressure renal portal vein controlled by muscular valve can be shunted toward afferent venous system or the vena cava based on need
- Bypasses glomerulus & provides 2/3 of blood supply to kidneys
- Enables up to 5x urate excretion than filtered load

Reverse peristalsis:
- Birds have a cloaca; a common orifice for GI, urinary and genital tracts
- Urine excreted via ureters into urodeal compartment of cloaca
- Uric acid excreted as colloidal solution with albumin; a high metabolic cost
- Albumin is degraded in GI tract and reused as energy source
- Urine is moved into the colon via reverse peristalsis
- Water & sodium reabsorption occurs within the GI tract

EFFLUENT EIGHT ROUND

Pick Your Champion for the Animal House 4 Region

Gila Monster vs Mourning Dove
Rapid Correction
Hyponatremia Correction & Osmotic Demyelination Syndrome (ODS)

- Consensus on slow correction of severe chronic hyponatremia has developed to avoid ODS
- Per US Guidelines:
  - Max 10-12 meq/L/24 hrs in average-risk patients
  - Min 4-6 meq/L/24 hrs in high-risk patients
- ODS is the result of osmotic damage to glial cells, when
  \[ \uparrow \text{ in intracellular tonicity (like in hyponatremia correction)} \]
  \[ \gggg \]
  ability of glia to adapt by taking in osmolytes (in alcohol use, malnutrition, hypophosphatemia etc.)
- Strict correction limits:
  - stole the spotlight from multifactorial nature of ODS
  - complicated hyponatremia management

Several “disruptor” papers recently challenged the status quo:
- suggested that ODS is ultra-rare
- that it is hardly ever associated with hyponatremia correction rate
- that slow correction rate is associated with worse outcomes

Central Pontine Myelinolysis (Classic variant of ODS):
- Characterized by piglet or trident signs in the pons on MRI,
- Finding can be delayed up to 3 weeks
Osmotic Demyelination Syndrome (ODS) in Patients Hospitalized with Hyponatremia

Multicenter cohort study
- 5 academic hospitals
- 22,858 hospitalizations with hyponatremia
  - Na <130 mmol/L
  - Mean initial serum sodium: 125 ± 4.6 mmol/L
- 68 years
- Average age
- April 1 2010 – December 31 2020

**Primary Outcome**
- Proportion with ODS identified by neuroimaging results and medical record review
- 12 patients (0.05%)
- 7/12 did not have rapid correction of serum sodium

**Secondary Outcome**
- Rate of overly rapid correction of serum sodium
  - >8 mmol/L in any 24-hour period
  - 3632 admissions (17.7%)

**Conclusion:** Rapid correction of serum sodium was common, but ODS was rare. Future studies with a higher number of patients with ODS are needed to better understand potential causal factors for ODS.

Is the rate of correction of hyponatremia associated with increased risk for mortality, length of hospitalization and central pontine myelinolysis (CPM)?

**Multicenter observational study**

3274 patients with admission sodium levels < 120 mEq/l

A correction rate of <6 mEq/l/24 hrs was associated with increased in-hospital mortality*

A correction rate of >10 mEq/l/24 hrs was associated with lower in-hospital mortality and shorter length of stay*

Correction rate:
- <6 mEq/l/24 hrs: 38%
- 6-10 mEq/l/24 hrs: 29%
- >10 mEq/l/24 hrs: 33%

7 patients with CPM were identified

5 of 7 with CPM despite sodium correction of ≤ 8 mEq/l/24 hrs
6 of 7 patients who developed CPM had alcohol use disorder, malnutrition, hypokalemia, or hypophosphatemia

**Conclusion:** Limiting the sodium correction rate was associated with higher mortality and longer length of stay. Whether the sodium correction rate influences neurologic complications needs further evaluation.


**VA by @brian_rifkin**
Slow Correction
We Do Not Need to Rethink Our Approach to Overcorrection of Hyponatremia

**The Study**
- Canadian Multicenter cohort
- Data from GEMINI Database

**Na <130**
- 22,858 hypoNa patients
- 86.9% Patients with Na ≥ 120 mmol/L
- Admission period April 2010 - Dec 2020

**Outcomes**
- 17.7% Rapid correction of Na (N=3,632)
- 0.05% Developed ODS (N=12)
- 7 of 12 with ODS did not have rapid Na correction

**Pitfalls**
- Majority of population had low ODS risk
- Only 265 patients had Na <110 (high risk for ODS)
- Self-induced water intoxication not excluded
- Definition of overcorrection not accurate
- ODS with negative MRI may have been missed

**Conclusion:** We should not relax our PNa correction limits and should continue to be wary of rapid correction for all patients with hyponatremia. Multicenter studies are needed to study patients with PNa < 105 mmol/L (population likely to have a high incidence of ODS). These studies should rely on meticulous chart review rather than diagnostic codes and radiologic findings, both of which can be misleading.


VA by @hellokidneyMD
More Thoughts Pro Slow Correction

• The “disruptor” papers would do well to beef up the rigor of their kinetics analysis

• They form a nice springboard for further investigations but offer only flimsy justification for abandonment of slow correction

• A Hyponatremia Intervention Trial (HIT) is currently ongoing; will answer the question whether poor outcomes of hyponatremia are due to hyponatremia itself, its treatment or the underlying disease

• For now, we should recognize ODS for the danger it is, appreciate its rarity while remembering its favored prey, and when compelled to act, heed the ancient wisdom of *festina lente*, or ‘haste makes waste’
EFLLUENT EIGHT ROUND

Pick Your Champion for the Hyponatremia Correction Region

Rapid Correction vs Slow Correction
Peritoneal Dialysis

Writer:
Timothy Hopper

Experts:
Janice Lea
Jeff Perl

Region Execs:
Matt Sparks
Jeff Kott
Peritoneal Dialysis First
• Patients who receive thorough pre-kidney failure education
  -45% choose peritoneal dialysis (PD) (Golper et al. NDT 2001)

• However, as of 2021 only 13% of patients starting dialysis are initiated on PD (USRDS)
PD First

- **Systems Challenges**
  - Pre-kidney failure education
  - Changes to the structure of outpatient dialysis units
  - Continued evolution towards value-based care
  - Starting individuals on peritoneal dialysis as the first modality

- **Approaches to achieve PD first**
  - Incremental PD - less-intensive PD start that factors in residual kidney function, mitigates the change to patients’ lifestyles while helping navigate the transition from stage 5 CKD to dialysis-dependence
  - Urgent Start PD - starting PD acutely just after PD catheter placement
  - PD Catheter Placement Timing
    - Tunneled PD catheter

- **Starting with PD as 1st modality has the potential to increase the number of patients receiving PD**
Conclusion: An urgent-start PD strategy during the transition of kidney failure to chronic dialysis is safe and has fewer complications commensurate with their reduced exposure to procedural risk than urgent-start temporary HD up to 6 weeks after dialysis commencement.


VA by @edgarvermamd
A simplified algorithm for initial PD prescriptions using an incremental approach

**Type of PD**
- **Automated PD (APD)**
  - Start with 2-3 exchanges
  - 1.5% dextrose or 1.5/2.5% combo
  - ~1200-1500 ml/exchange
  - Day time dry initially

- **Manual PD (CAPD)**
  - Start with 2-3 exchanges
  - 1.5% dextrose or 1.5/2.5% combo
  - ~1200-1500 ml/exchange

**Assessment**
- If volume overloaded or signs of underdialysis based on labs and clinical assessment:
  - **Suboptimal solute clearance**
    - Increase volume by 20%
    - Volumes >2000 ml may have little benefit
    - Increase exchanges if volume maxed
    - Limited APD exchanges to no more than 5
    - If APD maxed, day time dwell needed

  - **If volume overloaded**
    - Maximize diuretics
    - Ensure salt and fluid restriction
    - Use icodextrin
    - Adjust duration of dwell to maximize UF
    - Consider more hypertonic solution (2.5 or 4.25% as last resort)

**Revising Prescription**

Reference:

VA by @Nephro_Sparks X
Beyond Kt/V
Beyond Kt/V

- ISPD guidelines recommend a minimum threshold Kt/V of 1.7.
- Some advocate eliminating the measurement of Kt/V entirely because it does not have a clear impact on patient outcomes.
- Others consider Kt/V a useful measurement of small solute clearance that can call attention to changes in residual kidney function (RKF) or peritoneal membrane characteristics.
- There is no evidence to support that high-quality PD has a minimal Kt/V threshold.
- 2020 ISPD has concluded that the traditional focus on achieving a weekly Kt/V of at least 1.7 has been misplaced.
  - Importance of shared decision-making
  - Patient priorities: increasing flexibility with time/reducing fatigue, infections, mortality
Effect of Kt/V on Survival and Clinical Outcome in CAPD Patients in a Randomized Prospective Study

<table>
<thead>
<tr>
<th>Group</th>
<th>Kt/V</th>
<th>2-year Patient Survival</th>
<th>P-Value</th>
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</thead>
<tbody>
<tr>
<td>A</td>
<td>1.5 - 1.7</td>
<td>87.3%</td>
<td>0.9924</td>
</tr>
<tr>
<td>B</td>
<td>1.7 - 2.0</td>
<td>86.1%</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>&gt; 2.0</td>
<td>81.5%</td>
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Patients in group A: Kt/V 1.5-1.7

- Had inadequate ultrafiltration and dialysis
- Had a higher incidence of severe anemia

Conclusion: Patients with total Kt/V maintained below 1.7 had significantly more clinical problems and severe anemia but there was no difference in outcome demonstrated for patients with Kt/V maintained above 2.0 and between 1.7 and 2.0. We recommended that the minimal target of total Kt/V should be above 1.7.

Conclusion: Knowledge of the values or ranges for these various parameters that are associated with superior outcomes will help guide the nephrologist as she or he works jointly with individuals performing PD, assisting them in achieving their personal life goals.


VA by Jade Teakell @jmiteakell
EFFLUENT EIGHT ROUND

Pick Your Champion for the Peritoneal Dialysis Region

Peritoneal Dialysis First vs Beyond Kt/V
Things We Do For No Reason

Writer:
Imran Chaudhri

Experts:
Tony Breu
Lenny Feldman
Farrah Daccueil

Region Execs:
Jeff Kott
Samira Farouk
Phosphate Binders
Hyperphosphatemia Typically Develops in Patients with CKD Due To:
\[ \uparrow \text{Dietary Phosphate Load} + \downarrow \text{GFR} \]

Dietary restriction of phosphate is the initial management strategy
- Phosphate (PO\(_4^{3-}\)) binders can be used when dietary restriction not sufficient
- The goal in the outpatient setting is to lower elevated phosphorus levels “towards the normal range” (KDIGO) or aim for a Ca*Ph < 55 (KDOQI)

HyperP triggers a hormonal cascade, beginning with fibroblast growth factor 23 (FGF23), which has numerous adverse effects on the body:
- Abnormal bone remodeling
- Cardiovascular morbidity & mortality
- Worsening of acidosis & inflammation

Phosphate Binders:
- Bind enteric phosphate
- Are with each meal, only binding a certain amount of phosphate per meal
- Can be calcium-based or non-calcium based
Factors that affect serum phosphate level

**Decrease serum phosphate**
- Fibroblast growth factor 23
  - ↓ Urinary excretion
  - ↓ Intestinal absorption
  - ↓ Parathyroid hormone
- Dietary restriction
- Phosphate binders
  - ↑ Urinary excretion
  - ↓ Parathyroid hormone

**Increase serum phosphate**
- Low glomerular filtration rate
  (acute kidney injury, chronic kidney disease)
  - Urinary excretion ↓
- Vitamin D
- Increased phosphate load
  (diet, drugs, cell lysis)
  - Bone release ↑

**Conclusion:** Several factors influence serum phosphate levels. Among these, parathyroid hormone has a minimal effect on phosphate concentrations, as it causes both phosphate release from the bone and increases its urinary excretion.

**Reference:** Sekar et al. Phosphorus binders: The new and the old, and how to choose. Cleveland Clinic Journal of Medicine, 2018
Dietary Phosphate Consumption is Typically Lower in Hospitalized Patients

Patients in the hospital may have:
- Poor Oral Intake
- Diets Tailored to Kidney Function
- Continuous Tube Feeds

Phosphate binders only work on enteric phosphate in a bolus feed fashion:
- In hospitalized patients, their efficacy is limited
- They will not affect a phosphate load from intrinsic sources (e.g. Tumor lysis syndrome, catabolic state)

Phosphate binders have adverse effects:
- Contribute to pill burden (hospitalized patients may be already taking many medications)
- Are large and difficult to swallow (dysphagia is common in hospital)
- Cause GI side effects (Nausea, Vomiting, Diarrhea, Rarely Bowel Obstruction)
- Are Costly
Urine Anion Gap
Ammonium transport along the nephron

Conclusion: In the thick ascending limb, \( \text{NH}_4^+ \) is reabsorbed by the Na-K-2Cl transporter. In the collecting duct, Rh proteins mediate ammonia (\( \text{NH}_3 \))/\( \text{NH}_4^+ \) transport. The numbers depict the percentages of urinary total \( \text{NH}_3 \) at each site. Total \( \text{NH}_3 \) is concentrated in the medulla.

Reference: Adapted from Hamm et al. Acid - base homeostasis, CJASN, 2015

VA by @kriticism
Urinary Anion Gap (UAG) = Urinary (Na + K) – Cl

- **Urinary chloride is interpreted as surrogate for urinary ammonium** and thus is used to determine the kidney’s role in non-anion gap acidosis.

- A negative (-) UAG thus suggests gastrointestinal loss of alkali and preservation of the kidney’s ability to excrete acid (high urine Cl⁻) through the urine (Ne-“gut”-ive).

- A positive (+) UAG typically implies the kidney is unable to generate ammonium (NH₄⁺), leading to altered distal acidification of the urine (low urine Cl⁻).

- Direct urinary ammonium measurement is not widely available as the test is time-consuming & has been difficult to run...
The Many Limitations of the UAG Interpretation

It implies that there are no additional anions in the urine other than chloride

- In the setting of anion-gap metabolic acidosis, *anions such as lactic acid and ketones can be excreted* in the urine
- In toluene ingestion, *toluene metabolizes into the anion hippurate* which is excreted in the urine
- Proximal renal tubular acidosis leads to impaired bicarbonate (anion) reabsorption ⇒ *bicarbonaturia*
- In meat eaters: ↑dietary K⁺ intake + phosphate & sulfur-containing amino acids (metabolized to sulfuric acid) ⇒ *↑ UAG, but also increased urinary ammonium (NH₄⁺)*

**UAG use is limited in CKD**

- Impaired generation of NH₄⁺ with loss of kidney function
- Impaired reabsorption of additional anions (sulfites, other organic anions)
- Only a few studies directly correlate UAG with urinary NH₄⁺ across healthy, CKD, & kidney stone formers - and there is little correlation UAG & urinary NH₄⁺

- **Direct measurement of urinary ammonium is becoming easier!**
- **There has been a significant movement in the nephrology community to pettion laboratories to adopt direct measurement of urinary ammonium**
EFFLUENT EIGHT ROUND
Pick Your Champion for the Things We Do For No Reason Region

Phosphate Binders vs Urine Anion Gap
Antidotes and Supportive Therapies
Antidotes

- Over 2 million cases of human exposure to poisons were reported to the American Association of Poison Control Centers (AAPCC) in 2022

- Supportive care is always the first step, and it includes assessing vital functions and initial volume repletion for hypotension correction and toxin elimination (e.g., baclofen, methotrexate, lithium). Sodium bicarbonate enhances the elimination of certain poisons through urine alkanization (e.g. salicylates, methotrexate)

- Acetaminophen, the predominant cause of drug overdose in the US, is effectively countered by N-acetylcysteine (NAC), which inhibits CYP2E1 preventing N-acetyl-p-benzoquinone imine (NAPQI) formation and restoring glutathione function. Indications for use include:
  - Single ingestion >150 mg/kg or 7.5 grams
  - Unknown ingestion time with serum acetaminophen concentrations >10 mg/L
  - History of ingestion with any evidence of liver injury
Antidotes

- Fomepizole is a strong inhibitor of alcohol dehydrogenase (ADH), preventing the metabolism of toxic alcohols (e.g. methanol and ethylene glycol) into harmful metabolites

- Fomepizole is a potent inhibitor of CYP2E1 and may inhibit Jun-N-terminal kinase (JNK, an enzyme involved in hepatotoxicity, therefore, this antidote has also been used in high-risk acetaminophen poisoning

- Ethanol has a strong affinity for ADH and serves as an alternative to fomepizole when unavailable. Administered IV or orally, it aims to achieve an ethanol level of 100 mg/dL or ¼ to 1/3 of the serum methanol or ethylene glycol concentrations, expressed in mg/dL.

- For methotrexate (MTX) poisoning, **leucovorin** is the primary antidote as it bypasses the dihydrofolate reductase blockade induced by the poison. Urine alkalinization helps eliminate the drug. In cases of AKI and high drug concentrations (variable based on the time post-high dose MTX), **glucarpidase**, a recombinant bacterial enzyme that rapidly converts extracellular MTX into inactive metabolites, is typically needed, administered as a single dose of 50 units/kg.
Fomepizole for Ethylene Glycol and Methanol Poisoning

**Recommended Doses of IV Fomepizole for Ethylene Glycol or Methanol Poisoning**

- **Patients NOT on dialysis:**
  - Loading dose: 15 mg/kg, followed by 10 mg/kg q12 hr; after 48 hr, 15 mg/kg q12 hr

- **Patients on dialysis:**
  - Similar to earlier doses except it is given 6 hr after the 1st dose and q4 hr thereafter

**Criteria for Initiating Therapy in Known/Suspected Poisoning**

- **Ethylene glycol** (one of the following)
  - Plasma level ≥20 mg/dL (3.2 mmol/L)
  - Documented toxic amount ingestion and Osm gap of >10 mOsm/L
  - Suspected ingestion and ≥ 3 of:
    - Arterial pH level of <7.3
    - Serum CO₂ of <20 mmol/L
    - Osm gap of >10 mOsm/L
    - Oxalate crystalluria

- **Methanol** (one of the following)
  - Plasma level ≥20 mg/dL (6.2 mmol/L)
  - Documented toxic amount ingestion and Osm gap of >10 mOsm/L
  - Suspected ingestion and ≥ 2 of:
    - Arterial pH level of <7.3
    - Serum CO₂ of <20 mmol/L
    - Osm gap of >10 mOsm/L

**Reference:** Brent, Fomepizole for ethylene glycol and methanol poisoning. NEJM, 2009

**VA by @HusamJZ**
Extracorporeal Therapies
Extracorporeal therapies (ECTR)

• Hemodialysis (HD) was introduced in 1913 for salicylate clearance, but the ECTR’s role in poisoning management has regional variations and remains a topic of debate.

• The EXtracorporeal TReatments In Poisoning (EXTRIP) workgroup recommends ECTRs when there are clear signs of severe toxicity, impaired endogenous clearance, and plausible toxin dialysance.

• HD is the preferred ECTR, irrespective of hemodynamics due to its impact on drug clearance influenced by poison properties. Clearance is optimized using high-flux dialyzers, high blood flow, longer treatment times.
Extracorporeal therapies (ECTR)

• Continues Kidney Replacement Therapy (CKRT) is not the initial choice since its clearance is substantially lower than what a single session of hemodialysis can provide. CKRT after an initial HD session to manage the rebound can be a practical option (though re-dialyzing the patient is still preferred)

• Other less common ECTR options include the following:
  
  • Hemoperfusion removal via charcoal or resin cartridge

  • Therapeutic Plasma Exchange (TPE), separates plasma and exchanges it for albumin or fresh frozen plasma. It can be effective for highly protein-bound and large poisons

  • Peritoneal dialysis has a limited role in acute poisoning (max clearance <20 mL/min)
Extracorporeal Removal of Poisons and Toxins

Ideal Dialyzable Substance
- Small Molecule
- Low Protein Binding
- Low Vol of Distribution
- Rapid Movement Tissue → Plasma

Utility of Modalities in Poisoning

<table>
<thead>
<tr>
<th>Modality</th>
<th>Toxin Characteristic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Molecular Mass (kDa)</td>
</tr>
<tr>
<td>iHD</td>
<td>Up to 10-15</td>
</tr>
<tr>
<td>HCO Filter iHD</td>
<td>Up to 50</td>
</tr>
<tr>
<td>CRRT</td>
<td>Up to 15-25</td>
</tr>
<tr>
<td>Hemoperfusion</td>
<td>Unclear, but high</td>
</tr>
<tr>
<td>Plasma Exchange</td>
<td>No limit</td>
</tr>
</tbody>
</table>

Some dialyzable poisonings rarely require extracorporeal removal.
Some toxins have greater endogenous clearance than extracorporeal elimination can provide.

Conclusion: Improvements in technology have resulted in increased efficacy of removing drugs & other toxins with hemodialysis, & newer therapy modalities have expanded the role of extracorporeal supportive care of poisoned patients. The most frequently dialyzed poisons remain salicylates, toxic alcohols, & lithium; the extracorporeal treatment of choice for therapeutic removal poisons, when amenable, remains intermittent hemodialysis (iHD).


VA by Jade Teakell @jmteakell

*Patients with ESKD may accumulate certain opioids/metabolites & HD may be key to limiting toxicity.
EFFLUENT EIGHT ROUND

Pick Your Champion for the Toxicology Region

Antidotes and Supportive Therapies

vs

Extracorporeal Therapies
Metabolic Acidosis in CKD
Metabolic Acidosis in CKD

- Develops with lower GFRs due to diminished capacity to reabsorb bicarbonate and excrete ammonium

- CKD patients with metabolic acidosis have:
  - Adverse bone health
  - Decreased muscle mass
  - Progression of CKD
  - Higher incidence of cardiovascular events

- Bicarbonate supplementation can be given to neutralize excess acid and increase serum bicarbonate, but does it affect outcomes?

- Newer drugs recently developed (veverimer - hydrochloric acid binders) but outcomes not superior and agents not available
VALOR-CKD: Could veverimer slow progression of CKD in patients with metabolic acidosis?

**Methods**
- Randomized, double-blind, placebo-controlled trial
- Multicenter, 35 countries
- Veverimer: A novel, oral, polymeric hydrochloric acid binder
- Patients with:
  - eGFR 20-40 ml/min/1.73m²
  - Serum HCO₃⁻ 12-20 mmol/L
- Composite 1st Outcome = sustained eGFR decr ≥40% from baseline, ESKD, or renal death

**Results**

**Baseline**
- Mean Age 65.1 yr
- Women 42%
- Mean eGFR 29.1
- uACR 201 mg/g

**Per Protocol**

<table>
<thead>
<tr>
<th>Veverimer</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 week run-in, single-blind treatment with veverimer</td>
<td></td>
</tr>
<tr>
<td>To proceed to randomization:</td>
<td>serum HCO₃⁻ increase to ≥22 or ≥24 mmol/L from baseline</td>
</tr>
<tr>
<td>Median 26.7 months duration</td>
<td></td>
</tr>
<tr>
<td><strong>HCO₃⁻ at 3 mo.</strong></td>
<td><strong>1st Outcome</strong></td>
</tr>
<tr>
<td>22.0±3.0</td>
<td>20.1% (149/741)</td>
</tr>
<tr>
<td>20.9±3.3</td>
<td><strong>20.0%</strong> (148/739)</td>
</tr>
</tbody>
</table>


VA by Jade Teakell @jnteakell

**Conclusion:** VALOR-CKD recruited a large population of patients with metabolic acidosis with high risk for CKD progression. Treatment with veverimer did not slow CKD progression. The lower than expected bicarbonate separation may have hindered the ability to test the hypothesis.
Sodium bicarbonate tablets - 650 mg → roughly 8 mEq NaHCO3
Typical dose 2 tabs BID will provide about 30 mEq of bicarb/day

Can also reduce daily acid load by altering diet to include less animal protein and more fruits/vegetables
Animal protein → metabolized to sulfuric acid
Fruits/vegetables → metabolized to citrate

Encouraging fruits/vegetables in CKD:
- ameliorate metabolic acidosis
- lower BP
- improve HbA1C
- did not raise serum potassium in small trials
Metabolic Acidosis in AKI
## Metabolic Acidosis in AKI/ICU

### MUDPILES

- **M** ethanol
- **U** remia
- **D** iabetic ketoacidosis
- **P** araldehydes
- **I** soniazid
- **L** lactic acidosis
- **E** thylene Glycol
- **S** alicylates

### GOLDMARK

- **G** lycols (ethylene and propylene)
- **O** xoproline (pyroglutamic acidosis from Tylenol)
- **L** - lactic acidosis
- **D** - lactic acidosis (short gut syndrome)
- **M** ethanol
- **A** spirin
- **R** enal failure
- **K** etoacidosis (starvation, DKA)
Bicarbonate and RRT for Metabolic Acidosis in the ICU

Typically considered when pH < 7.2 due to animal studies showing reduced LV contractility and vasodilation/lower BP in animal studies
- However, limited human data (BICAR-ICU) does not show any mortality benefit in shock

Bicarbonate administration has the following effects outside of pH:
- volume
- hypernatremia if hypertonic bicarb (e.g. 4.2%) administered
- hypocalcemia
- hypokalemia
- increased pCO2

RRT for severe metabolic acidosis often required to deliver sufficient bicarbonate and prevent volume and electrolyte imbalances - higher doses 35 ml/kg/hr often required
- ICU trials looking at early vs late start RRT (e.g. AKIKI, STAART) show that metabolic acidosis is the primary indication for dialysis in approximately 20% of patients
Sodium bicarbonate therapy for patients with severe metabolic acidosis in the intensive care unit (BICAR-ICU)

Methods
- Multicenter ICU patients RCT, n=389
- Severe acidosis* and SOFA (4) or Lactate (>2mmol/L)
- Sodium bicarbonate infusion

Randomization

No Bicarbonate
- 28 Day Mortality + Organ Failure at day 7: 71%
- Use of RRT: 52%
- Composite Primary Outcome + AKI 2 or 3: 82%
- Survival at 28 days + AKI 2 or 3: 37%

Bicarbonate
- 28 Day Mortality + Organ Failure at day 7: 66%
- Use of RRT: 35%*
- Composite Primary Outcome + AKI 2 or 3: 70%
- Survival at 28 days + AKI 2 or 3: 54%*

*(p<0.0009) *(p<0.028)

Conclusion: In patients with severe metabolic acidosis, sodium bicarbonate had no effect on the primary composite outcome. However, sodium bicarbonate decreased the primary composite outcome and day 28 mortality in the a-priori defined stratum of patients with acute kidney injury.


VA by Verner Venegas @ Vernisartan
STARRT – AKI; Timing of Initiation of Renal-Replacement Therapy in Acute Kidney Injury

Methods

- Multinational Randomized Controlled Trial
- ICU pts Critically ill n = 3,019
- Severe AKI KDIGO STAGE 2 or 3

Standard strategy

- Until development of one or more criteria:
  - \( \geq 6.0 \text{ mmol/L, pH } \leq 7.20 \text{ or } \text{HCO}_3 \leq 12 \text{ mmol/L, } \text{PaFiO}_2 \leq 200 \text{ and perception of fluid overload, AKI for 72 hrs} \)
- 61.8\% Started RRT
- 43.7\% 6\%
- 16.5\%

Accelerated strategy

- Within 12 hours after patients had met full eligibility criteria
- 96.8\% Started RRT
- 43.9\% 10\%
- 23\%</p>

Conclusion: Among critically ill patients with acute kidney injury, an accelerated renal-replacement strategy was not associated with a lower risk of death at 90 days than a standard strategy.


VA by Verner Venegas @Vernisartan
EFFLUENT EIGHT ROUND

Pick Your Champion for the Metabolic Acidosis Region

Metabolic Acidosis in CKD vs Metabolic Acidosis in AKI
Liver-Kidney
Medical Eligibility Criteria For Simultaneous Liver-Kidney Transplant

Any one of these:

**Chronic Kidney Disease**
- eGFR 60 over 90 days
- eGFR < 30 post-kidney waitlist registration
- Dialysis for ESKD

**Acute Kidney Disease**
- Dialysis for 6 straight weeks
- eGFR < 25 for 6 straight weeks
- Combination of above two

**Metabolic Disease**
- Atypical HUS
- Hyperoxaluria
- Familial systemic amyloidosis
- Methylmalonic aciduria

**Conclusion:** Eligibility for simultaneous liver-kidney transplant includes confirmed CKD with persistent eGFR < 60, AKI requiring 6 weeks of dialysis or eGFR/CrCl < 25, and metabolic diseases like atypical HUS due to factor H/I mutations, hyperoxaluria, familial amyloidosis, or methylmalonic aciduria.


**VA by @DrPSVali**
AKI Prevalence is High Among Patients With Cirrhosis

- In 2021, 780 simultaneous liver-kidney (SLK) transplants (8% of all liver transplants) were performed for both adults & pediatric patients

- **Up until 2017, there were no standardized medical criteria to help make this decision**, raising concerns that high quality kidneys were being allocated to candidates who may have regained kidney function following liver transplant alone (LTA) – check out the new criteria introduced in 2017 on the next slide

- SLK-kidneys are usually **significantly higher quality** than those used for kidney transplantation alone, with a mean kidney donor profile index (KDPI) below 35% in 2014

- Determining the cause of AKI (and if kidney function will recover after LTA) in patients with cirrhosis is hard...and **distinguishing between hepatorenal syndrome (HRS), acute tubular necrosis (ATN), & other intrinsic kidney diseases is crucial**. The fractional excretion of sodium may not always help, and biopsies may be risky due to potential higher risk of bleeding.

- Recipients of SLK have lower rates of both acute cellular and antibody-mediated rejection, thought to be due to the **immunomodulatory properties of the liver on the immune system (antibody sink?!)**
Does kidney graft survival change with kidney-alone vs SLK or kidney-after-liver transplants (KAL)?

**Methods**

- **SRTR**: Scientific Registry of Transplant Recipients
- **United States**
- **Retrospective Cohort**
- **Aug 2017 – Aug 2022**

**Conclusion**: Over a 5-year period in the US, simultaneous-liver-kidney (SLK) transplantation was associated with significantly lower kidney graft survival compared with paired kidney-alone transplants. Most differences in graft survival between SLK and kidney-alone transplants occurred within the first year post-transplantation. By contrast, kidney-after-liver (KAL) transplants had comparable graft survival with paired kidney-alone transplants.

**Results**

- **1 yr**: N=3,053 Paired Donors Grafts
  - Kidney-alone Recipients: 94%
  - SLK Recipients: 89%
  - p<0.001

- **3 yr**: Kidney-alone Recipients: 86%
  - SLK Recipients: 80%

- **1 yr**: N=516 Paired Donor Grafts
  - Kidney-alone Recipients: 94%
  - KAL Recipients: 93%
  - p=0.53

- **3 yr**: Kidney-alone Recipients: 84%
  - KAL Recipients: 87%


VA by Jade Teakell @jmiteakell
Pancreas-Kidney
Diabetic Kidney Disease is the Most Common Cause of ESKD

- Individuals eligible for kidney transplantation who are also insulin dependent (T1 or T2DM) can be considered for one of the options below:
  - SPK (simultaneous pancreas-kidney) transplantation
  - Deceased donor kidney transplant alone (DDKA)
  - Living donor kidney transplant alone (LDKA)
  - Pancreas AFTER kidney transplant (PAK, typically after a LDKA)

- Immunosuppression for pancreas allografts is “off label” use and the 1st ever consensus conference for pancreas transplantation was held in 2019

- About 1,000 pancreas transplants were performed in the US in 2021: 80% SPK, 23% in those with T2DM. Recipients of PAK (after LDKA) have both increased kidney and pancreas allograft survival compared to SPK recipients

- Some anatomy: donor pancreas + a piece of their duodenum is goes into the recipient. Drainage of pancreatic enzymes (where the duodenum connects) can be either via the bladder or jejunum (“enteric”). Bladder drainage can lead to metabolic acidosis, cystitis, volume depletion...so 90% are now enterically drained

- Rates of early pancreatic graft failure (within 3 months) can be up to 10% - most common cause is thrombosis

- Pancreas rejection is usually asymptomatic & presents most commonly with ↑ serum levels of pancreatic enzymes (amylase, lipase). Inflammation impacts the exocrine component before causing islet cell injury. Treatment follows Banff criteria guidelines, as is done for kidney transplant rejection

- ↑ pre-transplant c-peptide levels (suggestive of higher levels of endogenous insulin production) may be associated with poorer post-transplant outcomes

- SPK is the “express lane” to kidney transplantation due to shorter wait times compared to DDKA alone
LDKT vs Simultaneous Pancreas-Kidney Transplant in Patients with T1DM: An Analysis of the OPTN/UNOS Database

**Compared to simultaneous pancreas-kidney transplantation (SPKT) n = 5,352**

**Living donor kidney transplantation (LDKT): n= 3,309**

- Had better kidney graft survival \( P=0.008 \)
- Had similar patient survival \( p=0.346 \)

**Deceased donor kidney transplantation (DDKT): n = 2,701**

- Had inferior unadjusted kidney graft & patient survival, partly due to favorable SPKT donor & recipient factors

**Conclusion:** Despite more transplants from older donors and among older recipients, LDKT was associated with superior outcomes compared with SPKT and was coupled with the least wait time and dialysis exposure. LDKT utilization should be considered in all patients with type I diabetes with an available living donor, particularly given the challenges of ongoing organ shortage.

**Reference:** Young et al. Living Donor Kidney versus Simultaneous Pancreas-Kidney Transplant in Type1 Diabetics: An Analysis of the OPTN/UNOS Database. CJASN, 2009

VA by @whatsthegfr
EFFLUENT EIGHT ROUND

Pick Your Champion for the Dual Organ Transplant Region

Liver-Kidney vs Pancreas-Kidney
From Your Effluent 8, Pick Your Filtered 4
From Your Filtered 4,
Pick Your Left & Right Kidneys
Crown your NephMadness 2024 CHAMPION:
Thanks for playing & good luck!

- Submit brackets by March 31, 2024, on Tourneytopia
- Claim CME and MOC credit through NKF PERC by May 31, 2024
- Discuss on social media using #NephMadness

Important Dates:
March 1, Friday (7:00 am Eastern): Bracket entry opens
March 31, Sunday (11:59 pm Eastern): Deadline for entering contest
April 2, Tuesday: Effluent 8 results
April 4, Thursday: Filtered 4 results
April 5, Friday: Left & Right Kidney results
April 8, Monday: NephMadness Champion crowned